REMARKS

Applicants infer from the Examiner's tacit lack of maintenance of the previous rejection under 35 U.S.C. 103(a) over Jespersen, et al., Eur. J. Biochem., 1994, 219, 365-373, in view of US patent 5,849,535 issued to Cunningham, and further in view of Houk, et al., J. Am Chem. Soc., 1987, 109, 6825-6836 that the rejection has been withdrawn by the Examiner.

New Grounds of rejection

Claim Rejections - 35 USC §103

Examiner's Rational

The Examiner alleges Claims 1-34 and 39-68 are as being unpatentable under 35 U.S.C. 103(a) over Jespersen, et al., Eur. J. Biochem., 1994, 219, 365-373, in view of Andersson, et al., Int. J. Peptide Protein Res., 1996, 47, 311-321, in view of US patent 5,849,535 issued to Cunningham, and further in view of Houk, et al., J. Am Chem. Soc., 1987, 109, 6825-6836.

The Examiner alleges Jespersen, et al, teaches the characterization of a trisulfide derivative of human growth hormone produced in E. Coli. The reference uses 1,4-dithiothreitol to reduce the full-length derivative of the growth hormone. The Examiner concedes the reference does not teach the pegylation of the protein, use of functional equivalents of other mercapto reducing agents and does not teach using the method for reducing the trisulfide impurity for antagonist.

The Examiner asserts Cunningham, et al., discloses a method for the preparation human growth hormone antagonist, B-2036 variants, that encompass the pegylation of the growth hormone. The Examiner concedes that Cunningham, et al. does not use mercapto compounds as reducing agents.

The Examiner argues Houk, et al., discusses the structure-reactivity relations for number of thiol compounds, which are functional equivalents of the compounds recited the instant application. The Examiner contends that the list of compounds can be used individually or in combinations of others for the purpose of reducing the disulfide bonds or trisulfide linkages.

The Examiner alleges Andersen et al., discloses the isolation and characterization of a trisulfide variant of recombinant human growth hormone rhGH hydrophobic variant

(rhGH-HV). The Examiner alleges the **amino acid sequence of the protein shown in Figure I (page 313), corresponds to SEQ ID NO:1** of the instant application (emphasis added). The Examiner alleges this **clearly establishes the presence of trisulfide bonds in SEQ ID NO: 1 of the instant application meeting a part of the limitation of claim 1** (emphasis added).

Applicant's Response

With all due respect Applicant deferentially asserts, contrary to the Examiner's statement, the amino acid sequence of the protein shown in Figure I (page 313), **DOES NOT** corresponds to SEQ ID NO:1. The amino acid sequence of the protein shown in Figure I (page 313) is that of hGH, which corresponds to **SEQ ID NO:2** of the instant application. Applicants have submitted herewith a copy of the sequence listing showing the nine differences between the amino acid sequence of SEQ ID NO:1 (amino acid differences circled) and the amino acid sequence on p 318 of Andersson et al (amino acids indicted by arrows).

Therefore, applicant's respectfully submits that the Office has failed to establish a *prima facie* case of obviousness and the rejection is improper.

Conclusion

Claims 1-34 & 39-68 are pending. Claims 69-76 have been withdrawn. Claims 35-38 have been cancelled. No new matter has been added. In view of the foregoing clarification it is respectfully submitted that all claims now pending in the present application are in condition for allowance. Therefore, swift passage of the application and claims to issue is respectfully requested.

Respectfully submitted,

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